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# Drug - Natural Product Interactions- Labeling Implications

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# Discussions on Drug Interactions

- **Publications of in vitro and in vivo drug interaction guidance documents**
  - *http://www.fda.gov/cder/guidance/clin3.pdf (1997)*
  - *http://www.fda.gov/cder/guidance/2635fnl.pdf (1999)*

- **Various public workshops/CDER rounds**
  - *Tucker, Houston and Huang, Clin Pharm Ther August 2001; 70(2):103*

- **PhRMA position paper/other publications**
  - *Bjornsson, Callaghan, Einolf, et al, J Clin Pharmacol, May 2003; 43(5):443*

- **Advisory Committee meetings**
  - *April 20-21, 2003 (CYP3A inhibitor classification and P-gp inhibiti*
  - *November 17-18, 2003 (CYP2B6 and CYP2C8- related interacti*
  - *November 3, 2004 (relevant principles of drug interactions)*

**Concept paper published - Oct 2004**

# Drug Interaction Studies — Study Design, Data Analysis, and Implications for Dosing and Labeling

**Draft guidance being cleared for public comment**

This guidance includes

current recommendations for *in vitro* and *in vivo* drug metabolism and drug interaction studies performed during drug development.

## Key messages:

1. Metabolism, drug-interaction info key to benefit/risk assessment
2. Integrated approach may reduce number of unnecessary studies and optimize knowledge
3. Study design/data analysis key to important information for proper labeling
4. Need to establish “Therapeutic equivalence boundaries” (no effect boundaries)
5. Labeling language needs to be useful and consistent


**1. recommends CYP2C8, along with CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A, in the routine assessment of metabolic interactions (inhibition, induction and metabolic profiling)**


**2. When evaluating metabolic inhibition *in vitro***

**- I/Ki greater than 0.1 would indicate further in vivo study**

**- recommends the use of 2 CYP3A substrates**


**3. Induction can be addressed in vitro**

**- starting with CYP1A2 and CYP3A (assumption: co-induction of CYP3A and CYP2C/2B)**

**- induction of greater than 40% of the positive control would indicate further in vivo study**


4. **includes tables of recommended probe substrates, inhibitors, inducers for in vitro and in vivo evaluation (these tables will be on the internet for future updates)**

**- suggests evaluation of PM vs EM in lieu of inhibition studies (CYP2D6, 2C9, 2C19)**

**- suggests evaluation of smokers vs non-smokers in lieu of induction studies (CYP1A2)**


5. Recommends classification of CYP inhibitors (all 6 CYPs)

   - strong, moderate, weak inhibitors (including grapefruit juice)

6. Defines sensitive substrates and substrates with NTR (for all 6 CYPs)


**7. Briefly discusses**

**-Protocol restrictions: use of dietary supplements, juices**

**-when the evaluation of multiple inhibitors may be appropriate**

**- use of cocktails for in vivo evaluation**

**- Labeling including St John's wort**


8. Provides a table of human transporters

9. Discusses in detail P-gp in vitro evaluation (substrate, inhibitor)

   - Provides 2 decision trees

10. Briefly discusses other transporters

# Key Questions To Ask On Drug-Drug Interactions:

1. Will an NME alter exposure to other drugs

2. Will other drugs alter exposure to the NME?

3. Are these alterations in exposure significant enough to warrant dose adjustment?

} Questions on Drug-Botanical Interactions

# Drug-Drug Interactions
# - Labeling Implications -

- **All relevant information…. should be included in the PHARMACOKINETICS subsection of the CLINICAL PHARMACOLOGY section of the labeling.**

- **The clinical consequences …. should be placed in DRUG INTERACTIONS, WARNINGS AND PRECAUTIONS, BOXED WARNINGS, CONTRAINDICATIONS, or DOSAGE AND ADMINISTRATION sections, as appropriate.**

- **When the data resulted in recommendations for dosage adjustments, contraindications, warnings, <u>these recommendations should also be included in "HIGHLIGHTS."</u>**

# Drug- Natural Product Interactions
# - Current Labeling examples -

*Physicians' Desk Reference at http://pdrel.thomsonhc.com/pdrel/librarian*
*A catalog of FDA approved drug products, http://www.accessdata.fda.gov/scripts/cder/drugsatfda/*
*CDER New and Generic Drug Approvals: 1998-2004, http://www.fda.gov/cder/approval/index.htm*

# Cyclosporine

**DOSAGE & ADMINSTRATION**

***Grapefruit and grapefruit juice*** **affect metabolism, increasing blood concentration of cyclosporine, thus should be avoided.**

# Fexofenadine

**Interactions with Fruit Juices**

***Fruit juices such as grapefruit, orange and apple*** **may reduce the bioavailability and exposure of fexofenadine. This is based on the results from 3 clinical studies using histamine induced skin wheals and flares coupled with population pharmacokinetic analysis. …… Therefore, to maximize the effects of fexofenadine, it is recommended that ALLEGRA-D 24 HOUR *should be taken with water***

*http://www.fda.gov/cder/foi/label/2004/21704lbl.pdf*

# Levonorgestrel and Ethinyl Estradiol

**Herbal products containing *St. John's wort (Hypericum perforatum)* may induce hepatic enzymes (cytochrome P 450) and p-glycoprotein transporter and may reduce the effectiveness of contraceptive steroids. This may also result in breakthrough bleeding .**

*http://pdrel.thomsonhc.com/pdrel/librarian/PFDefaultActionId/pdrcommon.IndexSearchTranslator#PDRPRE01el/2004/21704lbl.pdf*

# Isotretinoin

## CONTRAINDICATIONS and WARNING

**Patients should be prospectively cautioned not to self-medicate with the *herbal supplement St. John's wort* because a possible interaction has been suggested with hormonal contraceptives based on reports of breakthrough bleeding on oral contraceptives shortly after starting St. John's wort. Pregnancies have been reported by users of combined hormonal contraceptives who also used some form of St. John's wort (see PRECAUTIONS ).*1**

# Warfarin

## PRECAUTIONS

**Caution should be exercised when *botanical medicines (botanicals)* are taken concomitantly with COUMADIN. Few adequate, well-controlled studies exist evaluating the potential for metabolic and/or pharmacologic interactions between botanicals and COUMADIN. Due to a lack of manufacturing standardization with botanical medicinal preparations, the amount of active ingredients may vary. This could further confound the ability to assess potential interactions and effects on anticoagulation. It is good practice to *monitor the patient's response with additional PT/INR determinations when initiating or discontinuing botanicals.***



http://www.fda.gov/cder/foi/label/2005/009218s101lbl.pdf

# Warfarin (2)

**Information for Patients**

**Patients should be advised: Strict adherence to prescribed dosage schedule is necessary. Do not take or discontinue any other medication, including salicylates (e.g., aspirin and topical analgesics), other over-the-counter medications, and *botanical (herbal) products (e.g., bromelains, coenzyme Q10, danshen, dong quai, garlic, Ginkgo biloba, ginseng, and St. John's wort)* except on advice of the physician**



*http://www.fda.gov/cder/foi/label/2005/009218s101lbl.pdf*

# St John's wort Products

**WARNING: St. John's Wort can have potentially dangerous interactions with some prescription drugs. *Consult your physician* before taking St. John's Wort if you are currently taking *anticoagulants, oral contraceptives, antidepressants, anti-seizure medications, drugs to treat HIV or prevent transplant rejection, or any other prescription drug*.**

*FTC Warning ON Herbal Outlook or similar product (Panda), St. John's Kava Kava (ForMor), http://www.ftc.gov/opa/2001/06/cureall.htm*

## Related to Drug- Natural Product Interactions:

1. Metabolism, drug-interaction info key to benefit/risk assessment
2. Integrated approach may reduce number of unnecessary studies and optimize knowledge
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4. Need to establish "Therapeutic equivalence boundaries" (no effect boundaries)
5. Labeling language needs to be useful and consistent

NME's clearance pathway needs to be well-defined

Studies may not be needed- from known info

NME's exposure-response needs to be well-defined

# References


- Guidance for industry: In vivo metabolism/drug interactions: Study design, data analysis and recommendation for dosing and labeling (Issued 11/24/1999, Posted 11/24/1999); http://www.fda.gov/cder/guidance/index.htm; http://www.fda.gov/cder/guidance/2635fnl.pdf
- Tucker, Houston and Huang, Clin Pharm Ther August 2001; 70(2):103
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- Yuan, Madani, Wei, Reynolds, Huang, Drug Metab Disp, December 2002; 30(12) 1311
- Labeling guideline. Federal Register 65[247], 81082-81131. December 22, 2000.
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- FDA Advisory Committee for pharmaceutical sciences and Clinical Pharmacology Subcommittee meeting. Issues drug interaction concept paper. Rockville, MD. November 3, 2004; http://www.fda.gov/ohrms/dockets/ac/04/briefing/2004-4079b1.htm; http://www.fda.gov/ohrms/dockets/ac/04/slides/2004-4079s1.htm http://www.fda.gov/ohrms/dockets/ac/04/transcripts/2004-4079T1.htm
- Huang S-M, Lesko LJ, J Clin Pharmacology, June 2004
- Huang S-M, Hall S, Watkins P, et al, Clin Pharmacol Ther, Jan 2004
- Huang S-M, Temple R, Lesko LJ, in “Botanical – Drug Interactions, Scientific and Regulatory Challenges”, Ed, Lam F, Huang S-M, Hall S, Taylor and Francis, in press
- CDER Drug Interactions Website (under construction)

# Drug Interactions working group

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# Questions?